



Bladder Cancer

Current Practice in the Management of Superficial Bladder Cancer in the Netherlands and Belgian Flanders: A Survey

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Abstract

Objective: Because there is no national guideline for the diagnosis, therapy and follow up of (superficial) bladder cancer in the Netherlands and Belgium, the actual patient management may differ between urologists. The purpose of this study is to get insight in the current way urologists diagnose, treat and follow patients with superficial bladder cancer.

Methods: All practising urologists in the Netherlands ($n = 293$) and Flemish speaking Belgium (Flanders, $n = 223$) received a questionnaire with regard to the current management of patients with superficial bladder cancer. The results were compared with the guidelines provided by the European Association of Urology (EAU). Also a comparison was made between the two countries and between university and community hospitals.

Results: The results show a wide variation in current practice for superficial bladder cancer. Although the majority of urologists do not follow the EAU guidelines, current practice roughly matches these guidelines. There are no major differences between the two countries or between different types of hospitals. Discrepancies between current practice and guidelines are mostly too frequent use of techniques for the diagnosis, treatment and follow-up.

Conclusion: In all, there is a need for clear guidelines in superficial bladder cancer and an effective implementation of such guidelines into everyday practice.

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1. Introduction

Several studies have been published with recommendations on different aspects of management of

patients with bladder cancer. Unfortunately these recommendations are sometimes conflicting and therefore confusing. Therefore, international guidelines have been developed covering all fields of

superficial bladder cancer management. Important examples are those of the American Urological Association (AUA) and the European Association of Urology (EAU) [1,2]. The American recommendations were developed by an expert panel after review of the literature on bladder cancer from January 1964 to January 1998. The European guideline was also established after a critical appraisal of a systematic Medline literature research. Although the EAU guideline was published only 2 years after the AUA guideline, substantial differences can be noted between these guidelines. Not surprisingly, the actual practice concerning patients with bladder cancer differs between urologists. Recently a study was performed to study current surveillance practice of bladder cancer patients in the United Kingdom (UK) and Ireland [3], with the aim of initiating a debate on evidence-based guidelines for the long-term surveillance of bladder cancers. However, the answers to the short questionnaire sent to all consultant urologists showed a complete lack of consensus.

Because there is no guideline for the management of bladder cancer in the Netherlands and Belgium, the goal of this study is to provide data of current practice of diagnosis, treatment and follow-up of superficial bladder cancer patients in these countries. These data will be of help for the development of superficial bladder cancer guidelines.

2. Material and methods

2.1. Data collection

An extensive anonymous questionnaire was developed and sent to all practising urologists ($n = 516$) in the Netherlands ($n = 293$) and Flemish-speaking Belgium (Flanders, $n = 223$) who were registered by the Dutch and Belgian Urological Association. A draft questionnaire was developed and tested

among three expert urologists (academic and non academic). A Dutch questionnaire is available upon request. The survey explored the current policy of diagnosis, treatment and follow-up of superficial bladder transitional cell carcinomas. All questions were stratified for low-risk, intermediate-risk and high-risk tumours, according to EAU criteria [1]. The questionnaire allowed free-text, for further comments.

2.2. Statistical analysis

To analyse the data, the statistical software program SPSS version 10.0 was used. Frequency tables and cross-tabulations were obtained to indicate the (frequency and duration of the) used management techniques in the three riskgroups of superficial bladder cancers. All results were compared to the guidelines of the European Association of Urology.

3. Results

The response rate to the questionnaire was 50.6% ($n = 261$) of a total of 516 surveys sent out. Four questionnaires were received too late for analyses. Thirteen urologists stated not to treat patients with bladder cancer and were excluded from the study. Of all the respondents who indicated to treat bladder cancer patients, 63.1% ($n = 154$) worked in the Netherlands, 36.1% ($n = 88$) in Belgian Flanders and in 2 the country was missing. 14.3% ($n = 35$) of the urologists practised in a university hospital, 29.1% ($n = 71$) in a community training hospital and 55.7% ($n = 136$) in a community non-training hospital. Two questionnaires had missing data about the type of hospital.

Table 1 summarises the current diagnostic practice of superficial bladder cancer patients. All urologists, except one, use cystoscopy for the diagnosis of bladder cancer, although 7 urologists use ultrasound routinely and cystoscopy only when the ultrasound is negative or unclear. Other frequently used techniques are sediment and culture

Table 1 – The policy of consultant urologists in the Netherlands and Belgian Flanders ($n = 244$) for the diagnosis of (superficial) bladder cancer

Technique	No, never (%)	Yes, always (%)	Yes, in special cases (%)	Missing (%)
Cystoscopy	0.4	96.7	2.9	–
Photodynamic diagnosis	86.1	2.0	2.5	9.4
Outpatient clinic biopsy	68.4	7.0	17.6	7.0
Dipstick erythrocytes	55.3	32.4	2.0	10.3
Sediment and culture	2.9	86.5	7.8	2.8
Cytology	6.1	80.7	13.1	0.1
Urine marker	81.6	2.5	4.5	11.4
Blood examination	28.7	38.9	10.7	21.7
Ultrasonography kidney	15.6	59.4	18.0	7.0
Ultrasonography bladder	32.8	43.9	11.1	12.2
IVU	8.6	58.6	23.0	9.8
CT-scan	11.9	21.7	58.6	7.8

Table 2 – The policy of consultant urologists in the Netherlands and Belgian Flanders (n = 244) for the treatment of superficial bladder carcinomas besides TUR, stratified for risk group

Technique	Low-risk (%)	Intermediate-risk (%)	High-risk (%)
Bimanual examination before TUR	27.0	42.2	71.3
Bimanual examination after TUR	27.0	47.5	74.9
Deep biopsies (warm)	31.1	56.1	77.0
Resection border biopsies (warm)	12.3	31.2	50.4
Random biopsies (cold)	8.9	28.7	59.0
Second-TUR earlier than 3 months	4.9	22.1	84.8
Single instillation (chemo)	61.9	57.0	40.2
Instillation course (chemo/immuno)	29.4	91.7	94.6
Radiotherapy	0.4	6.5	34.8
Cystectomy	0.4	9.8	54.1

examination, cytology and IVU. Only 7.0% (n = 17) of all urologists use urine markers (sometimes). A CT-scan is used in special cases only, e.g. when an invasive tumour is suspected.

The policy for the treatment of superficial bladder carcinomas besides TUR is summarised in Table 2. With increasing risk category an increasing number of urologists use biopsies and bimanual examination for additional staging of the tumours. The majority of patients with low-risk superficial bladder tumours are treated with a single instillation of mitomycin-C (n = 126) or epirubicine (n = 40). Patients with intermediate-risk tumours are most frequently treated with a course of instillations or a single instillation. Instillation courses are mitomycin-C (n = 182), epirubicine (n = 52), and BCG (n = 63). In high-risk patients an instillation course is almost standard and a second TUR is very common. In these patients BCG instillations (n = 205) are more frequently used than mitomycin-C (n = 65). Also radical therapies are applied more often.

Table 3 summarises the current practice for follow-up. Cystoscopy is the standard follow-up method for all bladder tumours. Urinary sediment is used in approximately half of the patients, cytology between 60% and 90% depending on the risk category. Radiological imaging is increasingly used

Table 3 – The policy of consultant urologists in the Netherlands and Belgian Flanders (n = 244) for the follow-up of superficial bladder cancers

Technique	Low-risk (%)	Intermediate-risk (%)	High-risk (%)
Cystoscopy	97.5	98.7	98.7
Dipstick ery	12.7	12.7	13.1
Sediment	48.7	50.3	50.0
Cytology	59.4	83.2	92.2
Urine marker	4.1	6.1	7.3
Ultrasonography kidney	22.5	31.1	35.2
Ultrasonography bladder	16.3	18.4	18.8
IVU	17.2	35.2	52.4
CT-scan	5.7	15.5	40.9

Table 4 – The policy of consultant urologists in the Netherlands and Belgian Flanders (n = 244) for the total follow-up period for superficial bladder cancers

Total period	Low-risk (%)	Intermediate-risk (%)	High-risk (%)
2 years	11.1	0.8	0.0
5 years	51.2	25.0	10.2
10 years	25.0	45.5	22.5
Life long	11.5	27.9	66.4
Missing	1.2	0.8	0.9

in intermediate and high risk patients. Markers, again, are infrequently used.

The total period of follow-up for patients with low-, intermediate- and high-risk tumours is 5 years, 10 years and lifelong on average, respectively (Table 4).

In patients with low-risk tumours most urologists perform four cystoscopies in the first year of follow-up, two in the second year and one in the following period (Table 5). In intermediate-risk patients cystoscopy is typically applied four times in the first year, three times in the second year and two times in the following period. In high-risk patients, cystoscopy is applied four times in the first two years and two times in the following period.

Of all respondents, 52.5% indicated to leave small tumours of known low-risk patients and of older patients in the bladder until the next check-up. Alternatively, 59.0% of all urologists use outpatient coagulation to eliminate small tumours. Guidelines, such as EAU, EORTC and Comprehensive Cancer Centre Amsterdam (IKA), are used by 57.8%.

4. Discussion

Evidence based medical practice is an ideal situation. Policies are usually based on different levels of evidence from the literature, as judged by experts in the field. If evidence is clear and the experts are unanimous, such a policy is called a “standard”.

Table 5 – The policy of consultant urologists in the Netherlands and Belgian Flanders (n = 244) for the frequency of follow-up cystoscopies in low-, intermediate- and high-risk bladder cancers patients

		1 st year (%)	2 nd year (%)	Following years (%)
Low-risk	No	2.0	4.9	9.4
	Missing	1.2	1.2	2.2
	Yes (*)	17.6	16.8	16.4
	1x	2.5	11.1	43.4
	2x	13.1	44.7	26.6
	3x	15.6	17.2	1.6
	4x	48.0	4.1	0.4
Intermediate-risk	Not	2.9	3.7	4.9
	Missing	3.0	1.2	1.2
	Yes (*)	17.6	17.2	16.8
	1x	0.4	2.0	20.9
	2x	3.3	27.5	44.7
	3x	9.8	32.8	7.4
	4x	63.0	15.6	4.1
High-risk	No	3.7	5.3	4.9
	Missing	2.3	1.2	2.5
	Yes (*)	16.8	16.0	16.4
	1x	0.4	0.8	8.6
	2x	0.8	12.3	39.3
	3x	4.9	28.7	14.8
	4x	70.9	35.7	13.5
	>4x	1.2	0.0	0.0

(*): yes means: yes, but no frequency specified.

However, for many diseases literature does not provide sufficient evidence of the highest level. Moreover, experts are considered experts based on their extensive experience, but that does not necessarily mean that two experts agree. In this case the policy is called a “guideline”, which usually is a compromise based on generally accepted data. The advantage of a guideline is that it leaves more room for flexibility. On the other hand, two guidelines on one subject do not necessarily agree. This is clearly the case with the AUA and EAU guidelines on superficial bladder cancer [1,2]. Although there is only a little more than 2 years between the publication of these guidelines, several points are conflicting. The EAU guideline classifies patients into low, intermediate and high risk. Low risk patients are those with Ta, grade 1 and ≤ 3 cm single tumours, high risk are those with T1, grade 3, CIS, multiple or highly recurrent tumours. The AUA guideline makes a distinction between index patients 1 to 3: where index patients 1 have a bladder tumour not histologically confirmed yet, index 2 means any superficial tumour before intravesical therapy and index 3 means T1 or CIS after one course of intravesical therapy. The EAU advocates 1 immediate single instillation with chemotherapy in low risk patients. The AUA does not mention this at all. A course of intravesical

chemotherapy or immunotherapy is an option, but no therapy is advised. The EAU acknowledges that BCG can prevent progression. The AUA guideline does not, as it also does not support the use of maintenance BCG, the therapy of choice for CIS according to the EAU. Obviously, risk categorisation and risk adapted therapy advises do not match. Therefore, it is not surprising that the actual practice concerning patients with bladder cancer differs between urologists. In the UK and Ireland, for example, a short questionnaire was sent to all consultant urologists [3]. The answers showed a complete lack of consensus with regard to the long-term surveillance of bladder tumours. Although Joudi et al concluded in 2003 that in the US practice preferences for the management of superficial bladder cancer were in general agreement with the AUA recommendations [4], this is in contradiction with other reports. Surveillance policies in 6717 superficial bladder cancer patients were studied with information from the SEER database [5]. Surveillance procedures differed substantially from standard recommendations in clinical guidelines. Defining five 6-months intervals, starting at month 7 after resection, only 40% of the patients had an examination during all five intervals. “Low intensity surveillance” was related to older age, non-white race, favourable tumour histology, and high co-morbidity. Co-morbidity was also the only factor influencing therapy for superficial bladder cancer in another multivariate analysis with SEER data [6]. In a recent multiple-choice questionnaire the differences between urologists in the US and Canada in the approach to bladder cancer were evaluated [7]. IVU and cystoscopy were more popular in the US, as compared to ultrasound in Canada. In both countries adjuvant therapy for Ta lesions was not given in approximately 40%. Also significantly different was the recommendation for cystectomy in T2 disease in the US (74%) and Canada (34%). The authors concluded that the study showed a trend of US urologists toward more aggressive screening, closer surveillance, an earlier trigger for cystectomy, and more common indications for intravenous chemotherapy.

In all, diagnosis, therapy and follow up of (superficial) bladder cancer are subject to much variation. In order to see whether this is also the case in the Netherlands and Belgian Flanders, or whether these urologists follow guidelines such as the EAU guidelines, we studied their management with an extensive anonymous questionnaire. Moreover, the answers could be of help in case a national guideline will be made.

The study had a response rate of 50.6%. This is less than in the study from the UK and Ireland, where 501 questionnaires were sent (516 in our study), of which 365 (73%) was returned [3]. In the study from the US and Canada, however, only 32.3% and 40% of the questionnaires were returned, respectively [7]. Therefore, the results in our study may have been affected by non-response. However, it is expected that especially urologists who do not treat bladder cancer patients are among the non-responders and they will not influence the results. Because 57.8% of the respondents declare they already use guidelines, especially those of the EAU ($n = 57$), a comparison with the EAU guidelines is made.

4.1. *Diagnosis of bladder cancer*

The EAU considers both IVU and ultrasound adequate in the diagnostic setting. In this study IVU is applied more often than ultrasound (Table 1). Since only 7 urologists used ultrasound only, patient comfort does not seem to be a major item. Reimbursement issues can also influence the choice of techniques. However, although reimbursement is different in Belgium and the Netherlands, policies in both countries are comparable. Therefore, the impact of financial issues appears limited. In accordance to the EAU guideline, cytology is used by 93.8% of all urologists. Urinary markers are still used only sporadically. According to several recent reviews indeed evidence at this moment is insufficient to substitute cystoscopy by any of the currently available urine marker tests [8]. Other procedures are used sporadically. In all, the diagnostic procedure is according the guideline.

4.2. *Treatment of bladder cancer*

According to the EAU guidelines, bimanual examination should be performed to assess the clinical stage before and after TUR. Although improved imaging techniques give better and better staging information, it is usually done after TUR which makes it more difficult to interpret. Therefore, bimanual examination remains simple but valuable. After TUR deep biopsies of the tumour and suspected area should be taken to map the extent of the disease. Apparently procedures like this are tailored to the patients risk profile (Table 2), but even in high risk patients not more than 70 to 80% of the urologists follow the guidelines in this respect. A single instillation after TUR is able to reduce the recurrence rate significantly, and is strongly advocated by European experts [9]. In this study, still

38.1% of the urologists do not use a single instillation in the treatment of low-risk bladder cancer. Some use an instillation course instead and overtreat their patients, while others only perform TUR and under-treat. Other procedures, like adjuvant BCG in these patients, are anecdotally mentioned. BCG is probably indeed used for low-risk patients, since this was also found by Obek et al, who reported that in community practice in the US the use of BCG for low-grade TCC appeared to be quite common [10]. In intermediate-risk patients an early instillation is used in 57.0%, but almost all urologists use an instillation course with chemotherapy. Since one immediate instillation is also advocated in these patients, this is obviously one of the points that needs extra attention. In high risk patients most urologists (94.6%) use an instillation course, predominantly (maintenance) BCG. Early cystectomy in high-risk tumours is still a matter of debate because of the risk of progression, but could be favoured in special cases, depending on the state and age of the patient [11–13]. In this study early cystectomy increases with the risk profile, although mostly on special indication. In general therapy choices match the European guidelines, with a tendency to over-treat.

4.3. *Follow-up of bladder cancer*

Cystoscopy remains the gold standard for follow-up after TUR, and the first cystoscopy gives important prognostic information. Still, less invasive follow up in low risk patients is a point of discussion for years already. In this study only four urologists indeed do not use cystoscopy in low-risk patients. Three of these use ultrasound in stead; one uses sediment and dipstick examination. In low risk patients the EAU advises 2 cystoscopies the first year and then yearly for up to five years. Although most urologists indeed follow these patients for five years, half of them use more frequent cystoscopies than advised. Cytological samples often fail to demonstrate abnormalities in low-grade bladder cancers and are therefore not recommended [14]. Still, more than half of all urologists use cytology in the follow-up of low-risk patients. Many studies in the last few years have focused on the value of urinary markers. Most markers have a higher sensitivity than cytology, although predominantly because of detection of low-grade tumours [8,15]. Sensitivity of markers for CIS is even surprisingly low and specificity is always lower than cytology. In all, these tests cannot replace cystoscopy. Although several tests are commercially available the results of this study indicate that few urologists use them. Three

urologists did not use cystoscopy in intermediate or high-risk tumours. They used ultrasound and cytology in stead.

In high risk tumours the EAU guidelines recommend cystoscopy four times in the first two years, every four months in the third year, every six months in years 4 and 5 and then yearly continued lifelong. The results of this study largely resemble the EAU guidelines, but 33.0% of the respondents discontinue cystoscopy too early. Cytology is recommended for these patients, and is used by 92.2% of all respondents. Since the occurrence of upper urinary tract tumours during follow-up of superficial bladder cancer is rare, an IVU is not advised [16]. The highest frequency can be expected in CIS, and therefore IVU is indicated when cytology remains positive in spite of treatment of bladder CIS [17]. Still, 52.4% of the urologists routinely use IVU in the follow-up of high-grade tumours.

In all, follow up tends to be too intensive, especially in low risk patients, while it is discontinued too early by one third in high-risk patients. Apparently the distinction between the different risk groups is not adequately applied in follow-up. The extensive use of cytology in low and intermediate-risk patients is unnecessary.

4.4. EAU guidelines

57 urologists indicate they follow EAU guidelines. Their answers were compared to the guidelines and to the average results described above. In the diagnosis of bladder cancer these urologists all use a second TUR in high-risk bladder cancer patients, but not all use a bimanual examination. In the treatment, the most noticeable difference is that more urologists use single instillations and all use an instillation course in high risk patients, but some overtreat their patients by applying an instillation course in low-risk patients. The most striking difference in the follow-up is the frequent use of IVU and ultrasound, not recommended by the guidelines. Finally, fewer urologists discontinue follow-up too early.

4.5. Country and type of hospital

The policies between the different hospitals and countries largely match. This makes lack of communication or education between teaching and practicing urologists as a cause for differences unlikely. However, some dissimilarities occur. Diagnostic ultrasound is more often used in community non-training hospitals and in Belgian Flanders, whereas diagnostic dipsticks and blood examina-

tions are more applied in the Netherlands. Bimanual examination for staging is particularly applied in the Netherlands. Deep biopsies, on the other hand, are more often used in Belgian Flanders. Cystectomy as primary therapy is mostly applied in the Netherlands. In follow up especially urologists of university hospitals use outpatient coagulation and leave small tumours of low-risk patients and older patients in situ until the next check-up.

5. Conclusion

Diagnostic, therapeutic and follow up policies in the Netherlands and Belgian Flanders largely match the EAU guidelines. Although some urologists under-treat patients, discrepancies concern mostly a too frequent use of techniques for the diagnosis, treatment and follow-up of superficial bladder cancer with all the cost implications and the inconvenience caused to patients. Urologists who indicate to follow the EAU guidelines indeed adhere better to the guidelines. Still, deviation from guidelines based on a particular case and experience of the urologist always is possible. The differences between different hospital settings are limited, as is the case for differences between Belgian Flanders and the Netherlands. In all, it seems obvious that there is a need for clear guidelines and implementation of these guidelines in the management of superficial bladder cancer. Hopefully this paper is of use for these guidelines, in addition to the given general public health information.

References

- [1] Oosterlinck W, Lobel B, Jakse G, Malmstrom PU, Stockle M, Sternberg C. Guidelines on bladder cancer. *Eur Urol* 2002;41:105–12.
- [2] Smith Jr JA, Labasky RF, Cockett AT, Fracchia JA, Montie JE, Rowland RG. Bladder cancer clinical guidelines panel summary report on the management of nonmuscle invasive bladder cancer (stages Ta, T1 and TIS). The American Urological Association. *J Urol* 1999;162:1697–701.
- [3] Wazait HD, Al Bhueissi SZ, Patel HR, Nathan MS, Miller RA. Long-term surveillance of bladder tumours: current practice in the UK and Ireland. *Eur Urol* 2003;43:485–8.
- [4] Joudi FN, Smith BJ, O'Donnell MA, Konety BR. Contemporary management of superficial bladder cancer in the United States: a pattern of care analysis. *Urology* 2003;62:1083–8.
- [5] Schrag D, Hsieh LJ, Rabbani F, Bach PB, Herr H, Begg B. Adherence to surveillance among patients with superficial bladder cancer. *J Natl Cancer Inst* 2003;95:588–97.

- [6] Snyder C, Harlan L, Knopf K, Potosky A, Kaplan R. Patterns of care for the treatment of bladder cancer. *J Urol* 2003;169:1697–701.
- [7] Chung D, Hersey K, Flehner N. Differences between urologists in United States and Canada in approach to bladder cancer. *Urology* 2005;65:919–25.
- [8] van Rhijn BW, van der Poel HG, van der Kwast TH. Urine markers for bladder cancer surveillance: a systematic review. *Eur Urol* 2005;47:736–48.
- [9] Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol* 2004;171:2186–90.
- [10] Obek C, Shelfo SW, Korman HJ, Soloway MS. Intravesical therapy for transitional cell carcinoma of the bladder: the community practice. *Urology* 1999;53:82–7.
- [11] Ghoneim MA, el Mekresh MM, el Baz MA, el Attar IA, Ashamalla A. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. *J Urol* 1997;158:393–9.
- [12] Esrig D, Freeman JA, Stein JP, Skinner DG. Early cystectomy for clinical stage T1 transitional cell carcinoma of the bladder. *Semin Urol Oncol* 1997;15:154–60.
- [13] Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J Urol* 2001;166:1296–9.
- [14] Brown FM. Urine cytology. Is it still the gold standard for screening? *Urol Clin North Am* 2000;27:25–37.
- [15] Lotan Y, Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. *Urology* 2003;61:109–18.
- [16] Holmang S, Hedelin H, Anderstrom C, Holmberg E, Johansson SL. Long-term followup of a bladder carcinoma cohort: routine followup urography is not necessary. *J Urol* 1998;160:45–8.
- [17] Solsona E, Iborra I, Ricos JV, Dumont R, Casanova JL, Calabuig C. Upper urinary tract involvement in patients with bladder carcinoma in situ (Tis): its impact on management. *Urology* 1997;49:347–52.